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Prediction & Assessment of Dermal Exposure
Annette L. Bunge, Ph.D.

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6. AUTHOR(S)
Richard H. Guy, Ph.D.
Annette L. Bunge, Ph.D.

7. PERFORMING ORGANIZATION NAMES(S) AND ADDRESS(ES)
The Regents of the University of California
University of California, San Francisco
School of Pharmacy, Dept. of Biopharmaceutical Sciences &
Colorado School of Mines

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13. ABSTRACT *(Maximum 200 words)*
The ultimate objective was to develop physicochemically and biologically relevant algorithms with which the rate and extent of absorption of a chemical following dermal contact can be accurately predicted for diverse exposure scenarios. The rational for the proposed approach is based on the fact that manifestations of toxicity (local and/or systemic) following cutaneous exposure requires the transdermal penetration of the chemical. The unique permeation barrier properties of skin ensure that the kinetics of percutaneous absorption will determine the severity and time-course of any potential hazard. The long-term objective of meaningful risk assessment following dermal exposure, therefore, requires that the rate of skin penetration in man be predictable. The specific aims of the project were: (1) to derive, from a comprehensive database of the percutaneous absorption/penetration literature predictive ("structure-activity") algorithms to calculate a chemical's steady-state permeability (and constitutive diffusion and partition coefficients) across the skin. (2) To test the predictions of the unsteady-state modeling in vivo in humans using novel non-invasive methodology (accelerator mass spectrometry and attenuated total reflectance infrared spectroscopy).

14. SUBJECT TERMS
Risk assessment, dermal exposure, skin permeation, predictive algorithms, toxicity

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le 11 novembre 1998

Dr. W. Kozumbo
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Bioenvironmental-science grant program; US Air Force

Grant No. F49620-95-1-0021, "Prediction and Assessment of Dermal Exposure"

Dear Dr. Kozumbo:

I herewith append the final progress report on the above-referenced grant. Should you require any additional documentation (e.g., reprints, preprints, copies of specific data, etc.), please do not hesitate to contact me at once.

As you aware, I am now based primarily in France, and I am enjoying the new environment. I believe that we have spent an exceptionally productive 4-year period working on the above-referenced grant, and both Professor Annette Bunge and I are immmensely grateful for the support provided by your office.

I hope that we have further opportunities to work together again in the not too distant future. With best wishes.

Sincerely,

Centre Interuniversitaire de Recherche et d'Enseignement
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Date: November 10, 1998 ***FAX No:*** **00.1.703-696-8449**

A: Dr. Walter KOZUMBO
U.S. AFOSR

#_1_ de _10_ page(s)

De: **Richard H. Guy, Ph.D.**

Bioenvironmental-science grant program; US Air Force

Grant No. F49620-95-1-0001, "Prediction and Assessment of Dermal Exposure"

Dear Dr. Kozumbo:

I herewith append the final progress report on the above-referenced grant. Should you require any additional documentation (e.g., reprints, preprints, copies of specific data, etc.), please do not hesitate to contact me at once. The original + two copies + a diskette will be mailed from here within the next few days.

As you aware, I am now based primarily in France, and I am enjoying the new environment. I believe that we have spent an exceptionally productive 4-year period working on the above-referenced grant, and both Professor Annette Bunge and I are immmensely grateful for the support provided by your office.

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1. **Cover Page**

PROGRESS REPORT, August 31, 1998

Bioenvironmental Science Grant Program

Grant Number: **F49620-95-1-0001**

Project Title: **Prediction and Assessment of Dermal Exposure**

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Co-Principal Investigator: **Annette L. Bunge, Ph.D.**
Colorado School of Mines

____
Principal Investigator
Title: **Professor**
Phone: **415-476-1226**

2. Objectives

The ultimate objective of this research is to develop physicochemically and biologically relevant algorithms with which the rate and extent of absorption of a chemical following dermal contact can be accurately predicted for diverse exposure scenarios. The rationale for the proposed approach is based on the fact that manifestation of toxicity (local and/or systemic) following cutaneous exposure requires the transdermal penetration of the chemical. The unique permeation barrier properties of skin ensure that the kinetics of percutaneous absorption will, to a very large extent, determine the severity and time-course of any potential hazard. The long-term objective of meaningful risk assessment following dermal exposure, therefore, requires that the rate of skin penetration in man be predictable.

The specific aims of the project, with the key tasks *italicized*, are:

(1) To derive, from a comprehensive database of the percutaneous absorption/penetration literature, which is maintained in the P.I.'s laboratory, predictive ("structure-activity") algorithms to calculate a chemical's steady-state permeability (and constitutive diffusion and partition coefficients) across the skin.

To extend the theoretical calculations to unsteady-state situations (i.e., short-duration contact), which are more representative of typical exposure scenarios.

(2) To test the predictions of the unsteady-state modeling *in vivo* in humans using novel noninvasive methodology (accelerator mass spectrometry and attenuated total reflectance infrared spectroscopy).

To explore application of the predictive and experimental models proposed to the assessment of dermal absorption in "complex" exposure situations, specifically including (i) the penetration of very lipophilic compounds (including their absorption from non-aqueous vehicles), and (ii) the delivery of chemicals following deposition in volatile solvents.

Overall, then, this project aims to address an important and unresolved issue of significant occupational health and environmental concern, namely: "To what extent does dermal absorption of toxic chemicals contribute to the overall risk associated with occupational and/or environmental exposure?"

3. Status of Effort & 4. Accomplishments

Significant progress has been accomplished towards the principal research objective of the project: To predict the dermal absorption of chemicals for a variety of exposure situations, including those from water, from non-aqueous, non-evaporating films, and from deposited films (liquid or solid). The strategy was first {1} to develop and validate methodology to predict chemical absorption from water, under both steady-state and unsteady-state conditions, and then {2} to extend the experimental and theoretical work to more complicated exposure scenarios (i.e., deposition from volatile solvents, and exposure to very lipophilic chemicals).

In the process of researching and understanding the skin absorption of chemicals, three computer databases have been developed: (1) a fully searchable citation database, (2) a database of full-text copies of all papers in the citation database, and (3) a database of skin permeability and permeant physicochemical data extracted from papers included in the citation database. These three databases are described below. Demonstration versions containing a portion of each of these databases have been

provided on a CD for examination. Although valuable individually, the three databases are, in our opinion, particularly powerful when used in combination. For example, the sources of all data in SkinProp are included in SkinBase and SkinLit.

SkinBase is a citation database (running under EndNote Plus available from Niles & Associates, Berkeley, CA) which presently consists of >5,600 records (from journals, books, serials, conference proceedings, disserations, and patents) pertaining to the skin absorption of chemicals. SkinBase includes full abstracts, MESH keywords, specific skin absorption keywords and CAS numbers. SkinBase is available as an EndNote library, which requires EndNote 2 Plus to run, or as a Refer format text file, which can be used with most bibliographic software packages.

SkinLit is an assembly of full-text copies of the papers cited in SkinBase. These articles are in pdf files and can be opened or downloaded using various platforms: PC, Macintosh or Unix. These files are readable using Adobe Acrobat Reader 3.0. At present, the online version of SkinLit is password protected and not generally available, although a smapling of the database can be demonstrated.

SkinProp is a database of measurements pertaining to skin absorption of chemicals (permeability coefficients and partition coefficients measured *in vitro* across human and/or animal skin from aqueous solutions), relevant physical property data (e.g., octanol-water partition coefficients ($K_{o/w}$), acid dissociation constants for dissociating chemicals (pK_a)), and other useful information such as chemical structure, molecular weight, molecular formula, and CAS number. The database operates under Microsoft Access 97, which is provided as part of the Professional Edition of Office 97. The current version contains almost 600 measurements (either permeability coefficients or partition coefficients) for more than 250 chemicals. The demonstration version contains about 110 measurements for 22 chemicals selected to illstrate the capabilities of SkinProp. SkinProp can be searched by chemical name (including an extensive list of alternate names), molecular formula, or CAS number. All skin absorption data included in SkinProp have been collected from the original reference, which is cited with each measurement. Abstracts for these references can be obtained using SkinBase, while full text articles are provided in SkinLit.

So that permeability coefficient and partition coefficient data are used most appropriately, SkinProp provides pertinent experimental details with each skin absorption measurement. For example, the database documents which skin layers were present during the measurement (e.g., stratum corneum, viable epidermis, and dermis), the source and handling of the skin (e.g., the body region taken from, whether it was removed surgically from a living donor or from a cadaver, whether it was used fresh or after freezing, etc.), the temperature, the pH). In some cases, not all of this information was provided in the original paper and the authors subsequently provided information in response to our inquiries. When it was necessary to calculate the tabulated skin absorption data from other data (e.g., permeability coefficient from the reported flux and concentration), this was documented. For ionizing chemicals, the unionized fraction of the chemical at the measurement pH was calculated. The adjusted values of the permeability coefficient and partition coefficient provided in SkinProp were calculated assuming that only the unionized form of the chemical contributes significantly. This adjustment was not performed on measurements for chemicals that were more than 90% ionized.

The experimental and theoretical achievements in the last phase of work on this project are summarised below in the form of a list of publications, together with illustrative "vignettes" of the specific research performed. The cumulative effort has focussed upon (i) a more complete and fundamental understanding of skin barrier function, and hence (ii) a significantly improved capability to predict percutaneous penetration and dermal risk following exposure; (iii) specific examination of the particular cases of cutaneous uptake of chemicals following contact with contaminated soil, and (iv) the unique case of metal-based compounds.

1. Current Status and Future Prospects of Transdermal Drug Delivery. R.H. Guy. Pharm. Res. 13, 1765-1769 (1996).

2. Homogeneous Transport in a Heterogeneous Membrane: Water Diffusion Across Human Stratum Corneum In Vivo. Y.N. Kalia, F. Pirot and R.H. Guy. Biophys. J. 71, 2692-2700 (1996).

The objective of this study was to determine whether a structurally heterogeneous biomembrane, human stratm corneum (SC), behaved as a homogeneous barrier to water transport. The question is relevant because the principal function of the SC *in vivo* is to provide a barrier to the insensible loss of tissue water across the skin. Impedance spectra (IS) of the skin, and measurement of the rate of transepidermal water loss (TEWL), were recorded sequentially *in vivo*, in human subjects, as layers of the SC were progressively removed by the serial application of adhesive tape-strips. The low frequency ($\leq$ 100 rad/sec) impedance of skin was much more significantly affected by tape-stripping than the higher frequency values; removal of the outermost SC layer had the largest effect. In contrast, TEWL changed little as the outer SC layers were stripped off, but increased dramatically when 6-8 μm of the tissue had been removed. It follows that the two noninvasive techniques probe SC barrier integrity in somewhat different ways. Equally, post-SC removal, recovery of barrier function, as assessed by increasing values of the low-frequency impedance, proceeded apparently faster than TEWL decreased to the pre-stripping control. The variation of TEWL as a function of SC removal behaved in a manner entirely consistent with a homogeneous barrier, thereby permitting the apparent SC diffusivity of water to be found. Skin impedance (low frequency) was correlated with the relative concentration of water within the SC, thus providing and *in vivo* probe for skin hydration. Finally, the calculated SC permeability coefficient of water, as a function of SC thickness, was calculated and correlated with the corresponding values of skin admittance derived from IS.

3. Measurement, Analysis and Prediction of Molecular Transport Across Human Skin In Vivo. F. Pirot, Y.N. Kalia, A.L. Stinchcomb, G. Keating, A.L. Bunge and R.H. Guy. Proc. Natl. Acad. Sci., USA 94, 1562-1567 (1997).

Attenuated-total-reflectance Fourier-transform-infrared spectroscopy has been used to rapidly and noninvasively quantify *in vivo* the uptake of a chemical into the outermost, and least permeable, layer of human skin (the stratum corneum). The objective of the experiment was to develop a general model to predict the rate and extent of chemical absorption for diverse exposure scenarios from simple, and safe, short-duration studies. Measurement of the concentration profile of the chemical in the stratum corneum, and analysis of the data using the unsteady-state diffusion equation, enabled estimation of the permeability coefficient and calculation of the time required to achieve maximal transdermal flux. Validation of the spectroscopic technique employed was established, and quantitation of chemical uptake into the stratum corneum was independently confirmed using trace amounts of radiolabelled chemical in conjunction with liquid scintillation counting and accelerator mass spectrometry. The results presented have significant pharmacological and toxicological implications as the novel technology lends itself both to the prediction of transdermal drug delivery, and the feasibility of this route of administration, and to the assessment of risk following dermal contact with toxic chemicals. The simplicity of the approach and its direct application *in vivo* in man represent major and unique advantages.

4. Dermal Absorption from Contaminated Soils. 1. Theoretical Descriptions. J.M. Parks, A.L. Bunge, D.L. Macalady and R.H. Guy. Risk Analysis (In press, 1998).

Dermal absorption of chemicals from contaminated soils is poorly understood. We present a mathematical model that mechanistically describes dermal absorption of organic chemicals from soils and provides a theoretical framework from which to examine and interpret experimental data. The derived equations (a) account for larger absorption rates during the initial exposure period, (b) acknowledge the hydrophilic barrier presented by

the viable epidermis to highly lipophilic chemicals, and (c) are sensitive to the influence of soil chemistry. The model predicts that the absorbed dose should not depend on soil loading if surface coverage is at least monolayer, that the absorbed dose should increase proportionally with the level of contamination if soil loading remains unchanged, and that the absorbed dose of chemicals with similar molecular weights, but different octanol-water partition coefficients, should be the similar. These and other model predictions are compared with experimental results in a subsequent paper. Finally, the form and predictions from this model are compared with those from previously published models.

5. Stratum Corneum Thickness and Apparent Water Diffusivity: Facile and Noninvasive Quantitation In Vivo. F. Pirot, E. Berardesca, Y.N. Kalia, M. Singh, H.I. Maibach and R.H. Guy. Pharm. Res., 15, 490-492 (1998).

Recently, it was shown that water diffusivity across human SC *in vivo* was independent of position in the membrane, i.e., that transport was homogeneous in this structurally heterogeneous membrane. The experimental proof for this deduction rested upon the results of TEWL measurements recorded as a function of repeated adhesive tape-stripping of the SC. Concomitantly, analysis of the data permitted facile determination of SC thickness and the deduction of an apparent average diffusion coefficient for water across the membrane. In this article, the procedure and data analysis developed is applied to a much larger cohort of subjects and a simpler interpretative methodology is then derived to greatly facilitate the experimental demands necessary for quantification of SC thickness and water diffusivity and permeability therein.

6. Infrared Spectroscopic and Differential Scanning Calorimetric Investigations of the Stratum Corneum Barrier Function. A. Naik and R.H. Guy. Chapter in *Mechanisms of Transdermal Drug Delivery*, pp. 87-162. Edited by R.O. Potts and R.H. Guy, New York, NY: Marcel Dekker, 1997.

7. Human Skin Penetration by Metal Compounds. J.J. Hostynek, R.S. Hinz, C.R. Lorence and R.H. Guy. Chapter in *Dermal Absorption and Toxicity Assessment*, pp. 647-668. Edited by M.S. Roberts and K.A. Walters, New York: Marcel Dekker, 1998.

8. Soil Contamination: Theoretical Descriptions, A.L. Bunge and J.M. Parks. In: *Dermal Absorption and Toxicity Assessment*, pp. 669-696. Edited by M.S. Roberts and K.A. Walters, New York: Marcel Dekker, 1998.

9. Ion Mobility Across Human Stratum Corneum In Vivo. Y.N. Kalia, F. Pirot, R.O. Potts and R.H. Guy. *J. Pharm. Sci.* in press (1998).

The aim of this study was to develop methods to determine ionic transport parameters, in particular ionic mobilities, across human stratum corneum (SC) *in vivo*. It has been shown previously that the SC, a structurally heterogeneous biomembrane, behaves as a homogeneous barrier to water transport, that is, water diffusivity does not vary as a function of position within the SC; in this work, therefore, the question posed was whether ion motion behaved similarly. Low frequency impedance measurements (1.61Hz) reported on the decrease of SC impedance as the barrier was progressively removed by serial adhesive tape-stripping. This corresponded to an increase in ionic mobility of approximately two orders of magnitude across the SC (from the external surface to the interior). Therefore, an algorithm was developed from the absolute impedance data to calculate ionic mobility as a function of position within (i.e., depth into) the SC. The mobilities deduced from the algorithm correlated well with water permeability across the SC. The data presented here are thought to be the first measurements of ionic mobility across human skin *in vivo*.

10. Chemical Release from Topical Formulations Across Synthetic Membranes. Infinite Dose. J.M. Parks, R.L. Cleek and A.L. Bunge, M. *J. Pharm. Sci.*, **86**: 187-192 (1997).

Many skin diseases are treated topically with drugs dissolved in ointment or cream vehicles. Experiments measuring the rate of drug release from topical preparations may provide useful information, particularly as a method for monitoring formulation quality control. In one such experiment, the topical formulation is placed on a synthetic membrane and the appearance of drug is monitored in the initially drug-free solution (the receptor solution) on the other side of the membrane. Commonly, the volume of vehicle provided is large, and the percent of the applied dose which penetrates through the membrane is small. In these experiments, the cumulative mass appearing in the receptor solution should become linear in . The slope of this line is theoreticaly related to the drug diffusion coefficient in the vehicle (D_{uv}). However, the physical meaning of the intercept has not been defined. We have determined the physical meaning of the -intercept when cumulative mass released data are analyzed as linear functions of . Also, we describe a procedure for determining D_{uv} from experiments measuring drug appearance in the receptor solution from a large volume of an unstirred, viscous vehicle such as a cream or ointment. To correctly determine D_{uv}, the experiment must proceed long enough that the cumulative mass of drug appearing in the receptor solution becomes linear in . We designate this as the long time criterion or t_{lt}. Using $t_{lag,sv}$ for the same membrane, t_{lt} can be estimated. Failure to meet this criterion should theoretically lead to estimated values of D_{uv} which are smaller than the true value.

11. "Dermal Uptake". A.L. Bunge and J. McDougall. In: *Exposure to Contaminants in Drinking Water:Estimating Uptake through the Skin and by Inhalation*, chapter 6, Ed. S.S. Olin, CRC Press, Boca Raton, FL (1998).

12. Characterization of Molecular Transport Across Human Stratum Corneum *In Vivo*. A. Naik, Y.N. Kalia, F. Pirot and R.H. Guy. Chapter in *Percutaneous Absorption*, Edited by R.L. Bronaugh and H.I. Maibach, New York: Marcel Dekker, in press, 1999.

13. *Metals and the Skin - Topical Effects and Percutaneous Absorption*. J.J. Hostynek, R.S. Hinz, C. Lorence and R.H. Guy. New York: Marcel Dekker, 1999.

In addition, there will be at least four additional papers resulting directly from the general thrust of the research supported by USAF. Three of these articles will deal with chemical uptake from soil (*in vivo* in man, and *in vitro* across human and mouse skin, as a function of concentration and soil loading) and will demonstrate an excellent correlation between the theoretical models proposed and the experimental results obtained. A fourth paper is concerned with dermal uptake of chemicals from volatile (evaporating) solvents, again *in vivo* in man; the data represent, to our knowledge some of the first quantitative estimates of chemical permeation under these difficult-to-study conditions.

Summary: We believe that our achievements during the course of this award have met, in large part, the original objectives identified at the beginning of the research. We would submit that these accomplishments are directly relevant to the mission of the bioenvironmental science grant program of the AFOSR. Furthermore, our work is of direct relevance and importance to other civilian research priorities within the U.S. EPA, the National Institutes of Health (particularly, NIEHS) the DoD and the DoE.

5. Personnel Supported

University of California - San Francisco

Richard H. Guy	Professor. *Principal Investigator.*	[Supported]
Robert S. Hinz	Research Associate.	[Supported]

Gilles Touraille	Graduate Student	[Supported]
Cynthia Lorence	Research Associate.	[Supported]

Colorado School of Mines

Annette L. Bunge	Professor. *Co-Principal Investigator.*	[Supported]
Kelly D. McCarley	Graduate Research Assistant	[Associated]

6. Publications

Current Status and Future Prospects of Transdermal Drug Delivery. R.H. Guy. Pharm. Res. 13, 1765-1769 (1996).

Homogeneous Transport in a Heterogeneous Membrane: Water Diffusion Across Human Stratum Corneum In Vivo. Y.N. Kalia, F. Pirot and R.H. Guy. Biophys. J. 71, 2692-2700 (1996).

Measurement, Analysis and Prediction of Molecular Transport Across Human Skin In Vivo. F. Pirot, Y.N. Kalia, A.L. Stinchcomb, G. Keating, A.L. Bunge and R.H. Guy. Proc. Natl. Acad. Sci., USA 94, 1562-1567 (1997).

Dermal Absorption from Contaminated Soils. 1. Theoretical Descriptions. J.M. Parks, A.L. Bunge, D.L. Macalady and R.H. Guy. Risk Analysis (In press, 1998).

Stratum Corneum Thickness and Apparent Water Diffusivity: Facile and Noninvasive Quantitation In Vivo. F. Pirot, E. Berardesca, Y.N. Kalia, M. Singh, H.I. Maibach and R.H. Guy. Pharm. Res., 15, 490-492 (1998).

Infrared Spectroscopic and Differential Scanning Calorimetric Investigations of the Stratum Corneum Barrier Function. A. Naik and R.H. Guy. Chapter in *Mechanisms of Transdermal Drug Delivery*, pp. 87-162. Edited by R.O. Potts and R.H. Guy, New York, NY: Marcel Dekker, 1997.

Human Skin Penetration by Metal Compounds. J.J. Hostynek, R.S. Hinz, C.R. Lorence and R.H. Guy. Chapter in *Dermal Absorption and Toxicity Assessment*, pp. 647-668. Edited by M.S. Roberts and K.A. Walters, New York: Marcel Dekker, 1998.

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Chemical Release from Topical Formulations Across Synthetic Membranes. Infinite Dose. J.M. Parks, R.L. Cleek and A.L. Bunge, M. *J. Pharm. Sci.* (submitted).

Ion Mobility Across Human Stratum Corneum In Vivo. Y.N. Kalia, F. Pirot, R.O. Potts and R.H. Guy. *J. Pharm. Sci.* in press (1998).

"Dermal Uptake". A.L. Bunge and J. McDougall. In: *Exposure to Contaminants in Drinking Water:Estimating Uptake through the Skin and by Inhalation*, chapter 6, Ed. S.S. Olin, CRC Press, Boca Raton, FL (1998).

Characterization of Molecular Transport Across Human Stratum Corneum *in Vivo*. A. Naik, Y.N. Kalia, F. Pirot and R.H. Guy. Chapter in *Percutaneous Absorption*,

Edited by R.L. Bronaugh and H.I. Maibach, New York: Marcel Dekker, in press, 1999.

Metals and the Skin - Topical Effects and Percutaneous Absorption. J.J. Hostynek, R.S. Hinz, C. Lorence and R.H. Guy. New York: Marcel Dekker, 1999.

7. Interactions/Transitions

(a) Conferences, etc.

6th International Conference on Contaminated Soil, Edinburgh, United Kingdom, May 17-21, 1998.

S.M. Arnold et al. Release kinetics of 4-cyanophenol from soil into cellulosic membranes.

Dermal Exposure Workshop. US Environmental Protection Agency, National Exposure Research Laboratory (NERL), Research Triangle Park, NC, September 17, 1998.

Perspectives in Percutaneous Penetration - 6th International Conference. Leiden, The Netherlands, Sept. 22-26, 1998.

R.H. Guy. Peptide delivery by iontophoresis.
G.D. Touraille et al. Uptake of 4-cyanophenol from soils, water and pure solids.

American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition, San Francisco, CA, November 15-19, 1998.

G.D. Touraille et al. Determining dermal absorption by tape stripping in vivo human stratum corneum: Experiments and Theory.
G.D. Touraille et al. In vivo and in vitro measurements of percutaneous permeability parameters.
B.E. Vecchia et al. Comparison of permeability coefficients for excised skin from humans and animals.

Society for Risk Analysis, Annual Meeting, Phoenix, AZ, Dec. 6-9, 1998.

A.L. Bunge. Effect of dose on dermal absorption from liquid and solid vehicles.

Symposium on the Impact of Pharmacokinetics in Modern Drug Development, San Francisco, CA, May 17, 1998.

R.H. Guy. Skin Barrier Function and Transdermal Drug Delivery

Seminars

A.L. Bunge. Dermal absorption of chemicals: Data analysis and prediction. University of Iowa, College of Dentistry, Iowa City, IA (April, 1998).

A.L. Bunge. Predicting dermal absorption from various media. United States Environmental Protection Agency, National Exposure Research Laboratory, Las Vegas, NV (August, 1998).

R.H. Guy. Prediction of percutaneous absorption. Centre International de Recherche Dermatologique, Sophia Antipolis, France (Feb. 1998).

R.H. Guy. Prediction of percutaneous absorption. Univ of Wales, Cardiff (Feb., 1998).

R.H. Guy. Mechanisms of Percutaneous Absorption. University of Lyon, France (March, 1998).

R.H. Guy. Why Doesn't Skin Leak? Department of Biopharmaceutical Sciences, University of California, San Francisco, CA (April, 1998).

(b) Consultative and Advisory Functions

Richard H. Guy

Member, Pharmacological Sciences Study Section, National Institute of General Medical Sciences, National Institutes of Health, Bethesda, MD.

Participant, Dermal and Ophthalmic Drugs Advisory Committee, U.S. Food & Drug Administration, Rockville, MD.

Annette L. Bunge

Scientific advisor U.S. Environmental Protection Agency, peer review of *Dermal Risk Assessment Interim Guidance, Supplemental Guidance to the Risk Assessment Guidance for Superfund.*

Member of the Working Group on the *Estimation of Dermal and Inhalation Exposures to Contaminants in Drinking Water*, organized by the International Life Sciences Institute of the Risk Science Institute through a Cooperative Agreement with the U.S. Environmental Protection Agency's Office of Water. This work has now been published in a book, *Exposure to Contaminants in Drinking Water: Estimating Uptake through the Skin and by Inhalation*, Ed. S.S. Olin.

(c) Transitions

Kim H-C Wang, formerly of the Exposure Assessment Group, Office of Health and Environmental Assessment, Office of Research Development, U.S. EPA, Washington, DC (on temporary assignment to U.S. EPA Region 2, New York, NY).

Curtis Dary, Environmental Monitoring Systems Laboratory, U.S. EPA, Las Vegas, NV

Robert Zendzian, Office of Pesticide Programs, U.S. EPA, Washington, DC
Note: Skinbase has been made available to US EPA personnel beginning with Robert Zendian. Procedures for internet transfer have been developed.

8. New Discoveries, Inventions, or Patent Disclosures

Skinbase was made available to EPA personnel; initial contact via Robert Zendzian. The combined databases, in modified form, were also demonstrated at the "Perspectives in Percutaneous Penetration" - 6th International Conference, Leiden, The Netherlands, Sept. 22-26, 1998.

9. Honors/Awards

Richard Guy was awarded, for his work in "reverse iontophoresis" and noninvasive glucose monitoring, the Prix Applications Médicales de l'Electricité, 1997 by the Institut Electricité Santé, Paris, France.